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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/405,920	09/24/99	CARILLO S	ST94037A-US

EXAMINER	
BECKERLEG, A	
ART UNIT	**PAPER NUMBER**
1632	8

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BROBECK, PHLEGER & HARRISON, LLP
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DATE MAILED: 03/28/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/405,920	CARILLO ET AL.	
	Examiner	Art Unit	
	Anne M Beckerleg	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 5
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other: .

DETAILED ACTION

Applicant's amendment and arguments received on 12/29/00 have been entered. Claims 18-29 are pending and active in the instant application. An action on the merits follows. Please note that the examiner in the instant application has changed.

Those sections of Title 35, US code, not included in this action can be found in the previous office action, paper no. 4.

Applicant's compliance with the conditions for receiving benefit of co-pending US application no. 08/737,953 is acknowledged.

Claim Rejections - 35 USC § 112

The rejection of claims 21, 22, and 28-29 under 35 U.S.C. 112, first paragraph, for lack of written description for parts of calpastatin of SEQ ID NO: 1 or SEQ ID NO:3 which inhibits the activity of calpain is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claim for reasons or record as discussed in detail below.

The applicant argues that calpain inhibitors were known in the art at the time of filing and that the sequence of human calpastatin, SEQ ID NO:1, is disclosed in the specification such that one skilled in the art could produce fragments of the nucleic acid sequence and fragments of its encoded amino acid sequence. However, as discussed in the previous office action, fragments of calpain inhibitors and fragments of calpastatin capable of inhibiting calpain and further regulating cellular levels of p53 have not been disclosed by the specification and were not reported in the literature at the time of filing. Further, neither the specification nor the prior art teaches which regions of calpastatin or any other calpain inhibitor are responsible for calpain inhibition and p53 regulation or provide guidance as to the physical characteristics of such fragments including amino acid or nucleic acid sequence. The applicant is reminded that the claimed invention as a whole is not adequately described if the claims require essential or critical elements which are not adequately described in the specification and which are not conventional in the art as of applicants filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998). Applicant's assertion that fragments can be made does not overcome the lack of description for functional fragments which can inhibit calpain and further regulate p53 protein in a cell. Therefore, only full length human calpastatin meets the written description provision of 35 U.S.C. 112, first paragraph.

The rejection of claims 18-29 under 35 U.S.C. 112, first paragraph, for scope of enablement is withdrawn in view of new grounds of rejection of the claims for lack of enablement under 35 U.S.C. 112, first paragraph, see below.

Claims 18-29 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification discloses methods for regulating cellular levels of p53 protein comprising administering to cells a vector comprising a nucleic acid encoding a protein or polypeptide which is an inhibitor of the activity of calpain. The specification further discloses that the protein inhibitor of calpain can be all or part of calpastatin, or leupeptin. While claims 26-29 are directed to vector and nucleic acid compositions, the specification clearly discloses that the use for these vectors is the regulation of p53 levels on tumors *in vivo*. It is noted that claim 29 specifically recites the intended use of the composition for intra-tumor administration. Thus, the vectors and compositions are properly included in this lack of enablement rejection based on how to use these vectors.

The specification does not provide an enabling disclosure for regulating cellular levels of p53 by administering any vector encoding any protein inhibitor of calpain by any mode of administration. The term regulating is very broad and encompasses any effect on the cellular level of p53 in any kind of cell. Calpain were well known in the art as part of the large family of proteinases contributing to the degradation of proteins in cells. The specification teaches that p53

protein is rapidly degraded in cells and links the activity of calpain to this degradation. The specification provides working examples showing that purified calpain protein can cleave p53 protein in an *in vitro* assay , and further demonstrates that the addition of purified calpastatin or other known inhibitors of calcium dependant proteinases can inhibit calpain *in vitro* and thus increase levels of non-degraded p53 protein. Neither the specification nor the prior art teaches of any other activity of calpain that could affect the level of p53 protein in cells or teach any other form of regulation of p53 cellular levels other than the inhibition of calpain dependant p53 degradation. Further, it was known at the time of filing that p53 is mutated in many kinds of tumor cells. In particular, some p53 mutations have been linked to the loss of the calpain cleavage site. The specification does not teach or demonstrate which mutations in p53 result in a protein that retains susceptibility to calpain degradation. It is also noted that the specification teaches that fragments of calpastatin can be utilized to inhibit calpain. Neither the specification nor the prior art teaches fragments of calpain inhibitors and fragments of calpastatin capable of inhibiting calpain or teaches which regions of calpastatin or any other calpain inhibitor are responsible for calpain inhibition. Thus, based on the art recognized activity of calpain as a proteinase, the presence of various mutated forms of p53 in different cell types, the specific teachings of the specification that the inhibition of calpain results in decreased degradation of p53, the lack of evidence for other forms of p53 protein regulation resulting from calpain activity, and the breadth of the claims, it would have required undue experimentation to practice the scope of the invention as claimed.

The specification does not provide an enabling disclosure for using any all vectors to express calpastatin or any other calpain inhibitor *in vitro* or *in vivo* in cells such that any effect on p53 cellular levels is observed. The specification discloses that numerous types of vectors can be utilized to deliver calpastatin or other calpain inhibitors to cells *in vitro* and *in vivo*. The specifications working examples, as noted above, utilize purified calpastatin protein in cell free *in vitro* assays. While the specification provides a working example which discusses the construction of a recombinant adenoviral vector encoding calpastatin, the specification does not provide any data regarding the activity of this vector, it capacity to infect and express calpastatin in any and all cells, and the level of calpastatin produced in the various cell types. Further, the specification does not provide any guidance concerning the level of calpastatin expression that correlates with an effect on p53 degradation in intact cells. The specification also teaches that the disclosed vectors can be administered *in vivo* for the purpose of increasing levels of p53 in tumor cells, particularly tumor cells with one mutated and one wild type copy of p53, such that apoptosis is induced. The specification fails to provide sufficient guidance for routes of vector administration such that tumor cells are transfected/transformed *in vivo*, or provide guidance as to the level of calpastatin expression and the level of inhibition of calpain dependant p53 degradation that correlates with increased apoptosis in the presence of mutated p53.

At the time of filing, the literature teaches the unpredictability of achieving therapeutic levels of expression of a transgene *in vivo* by either direct or indirect administration of a recombinant vector or cells transduced/transfected with a recombinant vector. Verma et al. states

that, "[t]he Achilles heel of gene therapy is gene delivery..", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Science, Vol. 389, page 239, column 3, paragraph 2). Verma et al. also teaches that," ... the lack of efficient delivery systems, lack of sustained expression, and host immune reactions - remain formidable challenges" in gene therapy, and particularly points out that, " [t]here are considerable immunological problems to be overcome before adenoviral vectors can be used to deliver genes and produce sustained expression", and that non-viral vectors ," suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) Nature, Vol. 389, page 239, column 1, paragraph 1, and column 3, paragraph 2; page 240, column 1, and page 241, column 2, paragraph 2). Verma also teaches that the choice of an appropriate enhancer-promoter combination is critical to the level and consistency of gene expression from a particular vector and that , " .. the search for such combinations is a case of trial and error for a given type of cell" (Verma et al. (1997) Nature, Vol. 389, page 240, column 2, paragraph 2, and column 3, line 1, see also Eck et al. (1996) Pharm. Basis of Ther. 77-101). Marshall et al. concurs, stating that, " difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall et al. (1995) Science, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1). Orkin et al. further states in a report to the NIH that, " .. none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated"

(Orkin et al. (1995) "Report and recommendations of the panel to assess the NIH investment in research on gene therapy", page 8, paragraph 2). Further, in terms of delivering vectors to tumors *in vivo*, Dachs et al. states that while advances in gene therapy have been made using viral and nonviral methods, effective and selective delivery of DNA to tumor cells remains a complex task due to a poor and disorganized blood supply, and high interstitial fluid pressure in the solid tumor (Dachs et al., page 314, column 1, paragraph 2).

Thus, in view of the high level of unpredictability in achieving therapeutic levels of gene expression in particular target cells, and the lack of guidance in the specification for the parameters affecting gene delivery, such as sites and frequency of administration, the dosage of transduced cells or recombinant DNA, appropriate promoter/enhancer combinations and the level of calpain inhibitor expression required to achieve an effect on p53 cellular levels, the lack or working examples, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to use the invention as claimed.

The applicant's arguments presented in response to the rejection of claims 18-29 under 35 U.S.C. 112, first paragraph in the previous office action have been fully considered as they pertain to the instant rejection of record, but have not been found persuasive in overcoming the instant grounds of rejection. The applicant argues that the therapeutic or clinical data is not required in order to obtain a patent, and that FDA standards of effectiveness are inappropriate in regards to the patentability of the instant claims, citing *In re Brana*. It is noted that the office has neither requested nor required clinical trials and that FDA standards of effectiveness have not been

applied to the instant case. The office has analyzed the specification in direct accordance to the factors outlined in In re Wands, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, and 5) the presence or absence of working examples, and presented detailed scientific reasons supported by publications from the prior art for the finding of a lack of enablement in the instant. It is also noted that case law including the *Marzocchi* decision sanctions both the use of sound scientific reasoning and printed publications to support a holding of non-enablement (see In re Marzocchi 169 USPQ 367, and Ex parte Sudilovsky 21 USPQ2d 1702). Further, the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). It is also pointed out that *In re Brana*, as quoted by applicants, states that if a compound exhibits some desirable pharmaceutical property in a standard experimental animal it has made a significant and useful contribution to the art. Such is not the case in the instant application. The specification fails to provide any *in vitro* or *in vivo* data using the disclosed vectors. Thus, for the reasons stated above, applicant's arguments are not deemed persuasive in overcoming the instant grounds of rejection.

The rejection of claims 18-28 under 35 U.S.C. 112, second paragraph, as being indefinite in regards to the recitation of "the activity of calpain" is withdrawn.

The rejection of claims 18-25 under 35 U.S.C. 112, second paragraph, as being indefinite in regards to the term "regulating" is maintained. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection of the claims for reasons or record as discussed below.

The applicant argues that the data in Figure 1 shows the regulation of p53 and that the term regulating is well known to those of skill in the art. However, the term "regulating" is extremely relative and as the claim does not provide a standard for ascertaining the requisite degree, the scope of the claim is unclear. The term "regulating" can read on any and all effects on the cellular level of p53. The specification and the data in Figure 1 only disclose that the calpain is associated with the degradation of p53 and that the inhibition of calpain can decrease p53 degradation. It is suggested that the applicant amend the claim to recite methods of inhibiting the degradation of p53.

Claim Rejections - 35 USC § 102

The rejection of claims 26-29 under 35 U.S.C. 102 as being anticipated by Nixon et al. is withdrawn in view of applicant's arguments.

The rejection of claim 29 under 35 U.S.C. 102 as being anticipated by Asada et al. has been modified to include claims 26 and 28.

Claims 26, and 28-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Asada et al. (1989) J. Enz. Inhib., Vol. 3, 49-56. The applicant claims a nucleic acid encoding all or part of calpastatin that has the capacity to inhibit, at least in part, calpain, formulated for intra-tumor administration; and a viral vector comprising a nucleic acid encoding a protein which is an inhibitor or calpain. It is noted that the intended use of the nucleic acid for intratumoral injection must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. See *In re Casey,* 162 USPQ 235 (CCPA 1967) and *In re Otto,*136 USPQ 458, 459 (CCPA 1963).

Asada et al. teaches a lambda phage viral vector encoding human calpastatin and an expression vector encoding human calpastatin (Asada et al., page 51, and page 53). Asada et al. also teaches that calpastatin inhibits calpain (Asada et al., page 49). Thus, by teaching all the elements of the invention, Asada et al. anticipates the instant claims.

The applicant argues that Asada does not teach that the disclosed human calpastatin can inhibit a calpain. The examiner respectfully directs the applicants to pages 49 and 53, where Asada clearly teaches that human calpastatin inhibits calpain. Applicant's arguments regarding the intended use of the nucleic acid for intratumoral administration is unpersuasive as the intended use of the nucleic acid is not given patentable weight unless the intended use results in a structural difference between the claimed invention and the prior art. Further, the office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural

and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Beckerleg, Ph.D., whose telephone number is (703) 306-9156. The examiner can be reached Mon-Thurs and every other Friday from 9:30-7:00. If the examiner is not available, the examiner's supervisor, Karen Hauda, can be reached at (703) 305-6608. General inquiries should be directed to the group receptionist whose phone number is (703) 308-0196. The official fax number is (703) 308-4242.

Dr. A.M.S. Beckerleg